EFFECT OF CO_2 INHALATION ON VENTILATION AND MECHANICS OF BREATHING IN MITRAL DISEASE

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Administration of different concentrations of CO_2 is known to cause an increase in respiratory minute volume. This increase of ventilation in healthy subjects is directly related to the height of the inspired alveolar carbon dioxide tension. It has been shown, however, that in patients with emphysema and in those with mitral valvular disease the increment of minute volume is smaller than in the healthy subjects (Donald and Christie, 1949; Prime and Westlake, 1954; Cherniack and Snidal, 1956; Pauli, Noe, and Coates, 1960). Various explanations have been proposed for this diminished response to CO_2 stimulation. Reduced responsiveness of the respiratory centre was assumed to be the cause by some authors (Donald and Christie, 1949; Prime and Westlake, 1954; Pauli *et al.*, 1960), while the importance of increased resistance to airflow as a causative factor was stressed by others (Cherniack and Snidal, 1956; Brodovsky, Macdonell, and Cherniack, 1960). Most reports dealing with the effect of CO_2 inhalation are based on the measurement of minute ventilation and CO_2 in alveolar air or arterial blood; actual measurements of compliance and total lung resistance during carbon dioxide stimulation were obtained only in normal subjects but not in patients with mitral valvular disease (Butler *et al.*, 1960). This paper deals with observations on these latter parameters in healthy subjects and in patients with mitral valvular disease.

SUBJECTS AND METHODS

Six healthy subjects and 8 patients with mitral valvular disease were studied. The control group consisted of 4 men and 2 women aged 18 to 35 years. The group of patients consisted of 4 men and 4 women whose ages ranged from 20 to 46 years. In all of them the diagnosis of mitral stenosis was made on the basis of the classical physical signs of the disease. In 2 patients a soft systolic murmur was audible at the apex, radiating to the axilla, raising the possibility of some regurgitation in addition to the predominant mitral stenosis. In no case were there any clinical signs of congestive heart failure. The chest radiographs showed enlarged right ventricle and dilated left atrium, bulging pulmonary artery, and increased vascular markings in the lung fields. There were no signs of marked pulmonary hypertension. The electrocardiograms showed either mild to moderate right ventricular preponderance or were within normal limits. The whole group was, therefore, rather homogeneous as to the severity of the mitral stenosis. The patients' functional capacity was either Class II or III according to the classification of the New York Heart Association.

All subjects were studied in the sitting position. The control studies in both groups were performed while breathing room air. During this period minute volume, lung compliance, and total lung resistance were determined, and an arterial blood gas sample was taken for oxygen saturation, carbon dioxide tension, and pH determinations. After a 30-minute rest period, the subjects of both groups breathed 5 per cent CO_2 in oxygen for a period of 18 minutes. At intervals of 3 minutes minute volume, lung compliance, and total lung resistance were measured. An arterial blood sample was taken at the cessation of inhalation of the gas

mixture. (Patients who were unable to breathe the 5 per cent CO_2 mixture for the full 18 minutes, as well as patients with an arterial oxygen saturation below 95 per cent while breathing room air, were excluded from this study.)

The lung compliance and the total lung resistance were determined by the method described by Mead and Whittenberger (1953), using an œsophageal balloon, and measuring flow, volume, and pressure, each recorded on a Sanborn direct writer M 150. Measurement of the volume was accomplished by electrical integration of the rate of flow signal. Subtraction of a voltage proportionate to lung volume from a pressure-flow trace, and subsequently a voltage proportionate to air flow from a pressure-volume trace, obtained on an oscilloscope, resulted in a straight line. The slopes of these lines represented the total lung resistance and compliance of the lungs. The reported values are the average of 4 consecutive measurements. The respiratory rate, tidal volume, and minute volume were calculated from the recorded volume trace. The arterial oxygen content and capacity and carbon dioxide content were measured by the method of Van Slyke and Neill (1924). The arterial blood carbon dioxide tension was obtained from the line charts (Van Slyke and Sendroy, 1928) on the basis of the known blood pH and plasma carbon dioxide content.

RESULTS

Healthy Subjects. The results of the arterial blood studies are shown in Table I. As could be expected, the average arterial O_2 saturation was 96 per cent, the Pa_{CO_2} was 40 mm. Hg, and the pH 7·40. After 18 minutes of inhalation of 5 per cent CO_2 in oxygen the arterial O_2 saturation rose to 100 per cent, the Pa_{CO_2} to 46 mm. Hg, and the pH dropped to 7·36.

TABLE I

ARTERIAL BLOOD STUDIES OF NORMAL SUBJECTS

Subject	Arterial oxygen saturation (%)		Arterial CO_2 tension (mm. Hg)		pH	
	Room air	5% CO_2 in O_2	Room air	5% CO_2 in O_2	Room air	5% CO_2 in O_2
N.M.	95	100	43	49	7·40	7·35
V.S.	96	100	38	46	7·39	7·34
F.M.	96	100	42	45	7·40	7·40
L.M.	95	100	42	47	7·40	7·33
R.M.	97	100	39	43	7·40	7·36
M.C.	97	100	38	43	7·40	7·35
Mean	96	100	40	46	7·40	7·36

TABLE II

VENTILATORY STUDIES AND MECHANICS OF RESPIRATION OF NORMAL SUBJECTS

Subject	Age (yr.) and Sex	Respiratory rate (respir./min.)		Tidal volume* (ml.)		Minute volume* (l./min./m.²)		Compliance of lungs (l./cm. H_2O)		Total lung resistance (cm. H_2O/l./sec.)	
		Room air	5% CO_2 in O_2	Room air	5% CO_2 in O_2	Room air	5% CO_2 in O_2	Room air	5% CO_2 in O_2	Room air	5% CO_2 in O_2
N.M.	25 M	18	21 (112)†	595	2380 (400)†	5·8	27·2 (469)†	0·19	0·18 (95)†	1·4	3·2 (229)†
V.S.	35 M	14	25 (179)	865	1730 (200)	7·0	24·4 (349)	0·23	0·22 (96)	1·2	2·0 (167)
F.M.	25 M	16	23 (144)	550	1790 (325)	5·0	22·2 (444)	0·23	0·26 (113)	1·3	2·6 (200)
L.M.	33 M	23	37 (161)	550	1200 (218)	7·1	24·8 (353)	0·20	0·18 (90)	1·6	3·0 (188)
R.M.	24 F	16	24 (150)	550	1350 (246)	5·6	20·6 (368)	0·18	0·20 (111)	1·6	2·6 (162)
M.C.	18 F	18	21 (112)	500	1450 (290)	5·2	24·4 (469)	0·19	0·19 (100)	1·6	3·0 (188)
Mean		18	25 (143)	600	1650 (280)	6·0	23·9 (409)	0·20	0·21 (105)	1·5	2·7 (189)
		$p < 0·001$		$p < 0·002$		$p < 0·001$		$p > 0·1$		$p < 0·001$	

* Volumes corrected to body temperature, ambient pressure, and saturated with water vapour (B.T.P.S.).
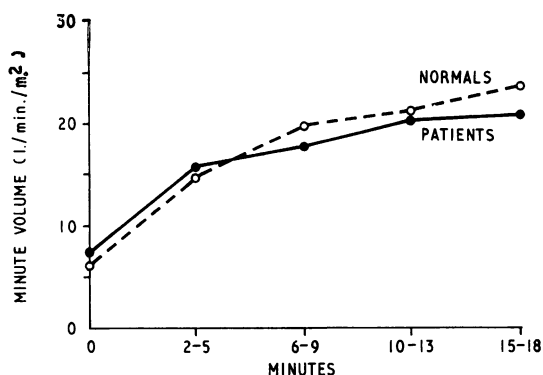† Figures in parentheses are percentages of control value.

FIG. 1.—Shows changes in minute volume during inhalation of 5 per cent CO_2 in oxygen in healthy subjects and in patients with mitral stenosis.
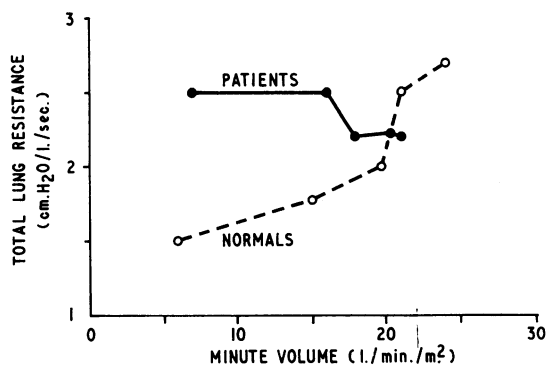
FIG. 2.—The minute volume is plotted against the total lung resistance during inhalation of the gas mixture. Note the rise of total lung resistance in the healthy subjects and the lack of rise in the patients.

The basal ventilatory measurements and the results of mechanics of respiration are given in Table II, together with the corresponding figures obtained following CO_2 inhalation. As can be seen, the minute ventilation rose from an average of 6·0 l./min./m.² to an average of 23·9 l./min./m.² as a result of CO_2 stimulation (Fig. 1). This rise is mainly due to an increase in tidal volume, and only to a lesser degree to a rise in the respiratory rate, since the tidal volume rose almost 3 times above the control value, while the frequency did not even double.

The lung compliance averaged 0·20 l./cm. H_2O on room air, and did not change during CO_2 inhalation. On the other hand, the total lung resistance which was 1·5 cm. H_2O/l./sec. on room air increased to 2·8 cm. H_2O/l./sec. following CO_2 stimulation (Fig. 2).

Patients with Mitral Stenosis. The average arterial O_2 saturation, Pa_{CO_2}, and pH values were within the normal range on room air. The response to 5 per cent CO_2 inhalation was not significantly different from that found in the group of normal subjects (Table III).

The minute volume averaged 7·0 l./min./m.² which is slightly higher than in the control subjects. Inhalation of 5 per cent CO_2 led to an increase of the minute volume from an average of 7·0 l./min./m.² to an average of 20·8 l./min./m.². This increase was less marked than in the healthy subjects, and was also mainly due to a rise in the tidal volume.

The average compliance of the lungs was somewhat lower than in the control group

TABLE III

ARTERIAL BLOOD STUDIES OF PATIENTS WITH MITRAL STENOSIS

Patient	Arterial oxygen saturation (%)		Arterial CO₂ tension (mm. Hg)		pH	
	Room air	5% CO₂ in O₂	Room air	5% CO₂ in O₂	Room air	5% CO₂ in O₂
T.D.	96	100	40	50	7·40	7·32
D.R.	97	100	40	48	7·33	7·25
M.E.	97	100	38	48	7·40	7·31
V.C.	95	100	43	46	7·40	7·38
N.R.	98	100	42	50	7·40	7·37
F.S.	95	100	37	48	7·45	7·37
P.E.	95	100	36	48	7·39	7·32
L.M.	95	100	37	46	7·40	7·32
Mean	96	100	39	48	7·40	7·33

TABLE IV

VENTILATORY STUDIES AND MECHANICS OF RESPIRATION OF PATIENTS WITH MITRAL STENOSIS

Patient	Age (yr.) and Sex	Respiratory rate (respir./min.)		Tidal volume* (ml.)		Minute volume* (l./min./m.²)		Compliance of lungs (l./cm. H₂O)		Total lung resistance (cm. H₂O/l./sec.)	
		Room air	5% CO₂ in O₂	Room air	5% CO₂ in O₂	Room air	5% CO₂ in O₂	Room air	5% CO₂ in O₂	Room air	5% CO₂ in O₂
T.D.	46 M	11	20 (182)†	835	1880 (225)†	5·0	20·2 (400)†	0·20	0·14 (70)†	2·2	1·6 (73)†
D.R.	35 F	20	28 (140)	595	1200 (202)	7·7	21·8 (283)	0·21	0·17 (81)	1·6	1·4 (88)
M.E.	46 F	21	26 (124)	480	1075 (224)	6·2	17·0 (274)	0·13	0·14 (108)	2·4	1·8 (75)
V.C.	34 M	18	24 (133)	650	870 (134)	6·1	10·8 (177)	0·23	0·23 (100)	2·4	2·9 (121)
N.R.	31 F	22	31 (141)	490	1085 (222)	7·0	22·0 (314)	0·13	0·07 (54)	3·7	3·6 (97)
F.S.	39 M	20	41 (205)	645	1400 (217)	7·4	32·8 (433)	0·12	0·16 (133)	2·2	2·0 (91)
P.E.	20 F	20	25 (125)	650	1100 (169)	9·5	19·9 (210)	0·08	0·09 (113)	2·8	2·0 (71)
L.M.	36 M	22	29 (132)	530	1290 (243)	6·8	21·4 (314)				
Mean		19	28 (148)	609	1238 (204)	7·0	20·8 (301)	0·16	0·14 (94)	2·5	2·2 (89)
		p<0·01		p<0·001		p<0·001		p>0·1		p>0·1	

* Volumes corrected to body temperature, ambient pressure, and saturated with water vapour (B.T.P.S.).
† Figures in parentheses are percentages of control value.

(0·16 l./cm H₂O), and did not change following inhalation of 5 per cent CO_2. A significant difference, as compared to the normal subjects, was found in the total lung resistance. The resting value averaged 2·5 cm. $H_2O/l./sec.$ which is an obviously pathological value and, in contrast to the response of the healthy subjects, it did not rise following inhalation of CO_2. Detailed values of the entire group are shown in Table IV and Fig. 1 and 2.

DISCUSSION

A raised alveolar CO_2 tension following inhalation of different concentrations of CO_2 leads to a marked increase in ventilation in healthy subjects. This rise is achieved mainly by an increase in tidal volume. Plotting different levels of arterial or alveolar CO_2 tensions against corresponding levels of total ventilation results in a stimulus response curve which is linear within the range of physiological stimulation and response (Alexander et al., 1955; Pauli, et al., 1960) (Fig. 3). However, responsiveness to CO_2 stimulus should be judged not only by the increment of ventilation, since this in itself may be altered by mechanical abnormalities of the lungs or airways (Brodovsky et al., 1960).

In healthy subjects, airway resistance was found to be unchanged during 10-minute inhalation of 4–6 per cent CO_2 (Butler et al., 1960). On the other hand, this gas was shown to cause an increase in total lung resistance (up to 54%) (Nadel and Widdicombe, 1962), increased dynamic P–V relation (Einthoven, 1892; Dixon and Brodie, 1903), and reduction in airway size on radiograph in different experimental animals (Kilburn, 1960). These changes were considered to be due to central stimulation, since they could be abolished by vagotomy. It has also been suggested, however, that CO_2 may act directly on the smooth muscle of small bronchi (Nisell, 1950; Severinghaus et al., 1961). Other authors described the effect of CO_2 on ventilation as a result of perfusion of the brain with blood containing an increased concentration of carbon dioxide, or as due to an increased P_{CO_2} of the cisternal cerebrospinal fluid (Lambertsen, 1963).

The hyperventilation induced by CO_2 inhalation in the healthy subjects is much more pronounced than in patients with chronic obstructive emphysema. One possible explanation for this phenomenon was a decreased responsiveness of the respiratory centre to the high concentration of CO_2 because of a pre-existing and sustained rise of CO_2 tension in the arterial blood of these patients (Donald and Christie, 1949). However, Cherniack and Snidal (1956) described a much diminished ventilatory response to CO_2 in healthy subjects after adding external resistance to air flow. Particular stress should be put on this finding that variations in ventilation may be caused by artificial change of the airway resistance without any alteration in the responsiveness of the respiratory centre.
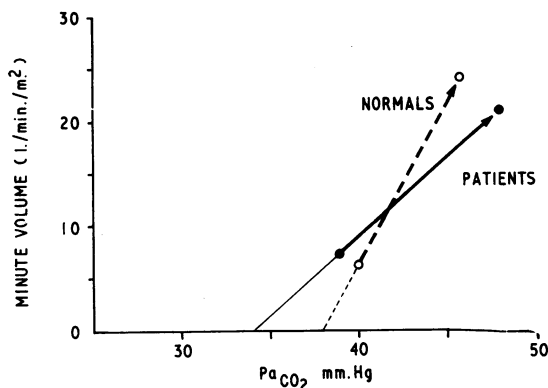
FIG. 3.—The relation between the Pa_{CO2} and the minute volume in 6 healthy subjects and 8 patients. Note the reduced responsiveness in the patients. Extrapolation of the two lines might indicate a diminished threshold of the respiratory centre for CO_2 stimulation.
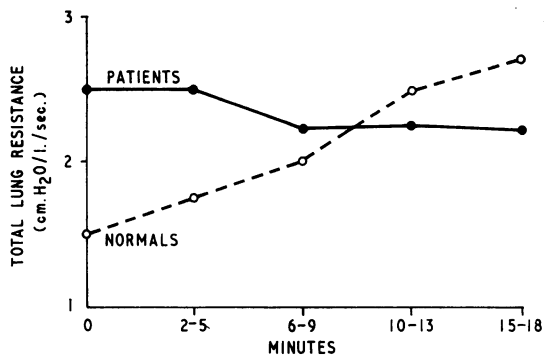
FIG. 4.—The change in total lung resistance during CO_2 inhalation is shown.

Further evidence supporting this suggestion was found by demonstrating an increment in ventilation in patients with obstructive emphysema following administration of a bronchodilator drug (Cherniack and Snidal, 1956).

Diminished ventilatory response to CO_2 stimulation, as in the emphysematous patients, was also described in patients with mitral valvular disease (Pauli et al., 1960). This similarity was found in spite of the difference in the resting arterial CO_2 levels in these two groups of patients. Since the patients with mitral valvular disease studied by Pauli et al. (1960) and those in our study had raised resting ventilation in the presence of a lowered Pa_{CO_2}, increased responsiveness of the respiratory centre to CO_2 inhalation was thought to be present, but could not be proved (Fig. 3). The importance of mechanical properties of the lungs by which the ventilatory response may be altered was not, however, considered. It is known that in mitral stenosis there is an increase in pulmonary vascular resistance, as well as congestion in the lungs and frequent respiratory tract infections. These factors, combined or separate, may lead to a decreased lung compliance and increased airway resistance (White, Butler, and Donald, 1958; Butler, 1960).

The aim of our present study was, therefore, to investigate the effect of CO_2 inhalation on the ventilation as well as on the mechanics of breathing in patients with mitral stenosis. Our results were similar to those described by Pauli et al. (1960) in regard to a diminished ventilatory response to CO_2 inhalation. Though the patients increased their minute ventilation to about threefold the control value, it was still lower than in the normal subjects.

In reviewing the results of the mechanics of breathing, two significant findings were observed. The total lung resistance at rest was much raised in patients with mitral stenosis. Together with this rise the lung compliance was somewhat lower in the patients than in the normal subjects, the difference not being statistically significant. These findings are in accordance with observations of White et al. (1958) and Butler et al. (1960).

In response to CO_2 inhalation, the normal subjects and the patients reacted differently. There was a statistically significant rise of total lung resistance in normal subjects with no change in lung compliance. This observation may indicate a diffuse constriction of the major airways during CO_2 inhalation. This finding is contrary to that reported by Butler et al. (1960) who did not find a rise in airway resistance. However, it should be noted that they administered the CO_2 mixture from 1 to 10 minutes only, while the pronounced rise in total lung resistance in our study appeared mainly during longer periods of inhalation of CO_2 (Fig. 4). We did not perform any special investigations in order to define the site of action of CO_2, i.e. whether the gas acted directly on the bronchial

musculature, whether it caused constriction through a reflex arch, or whether the raised Pa_{CO_2} or cH had a central effect.

Inhalation of CO_2 may lead to hyperventilation without necessarily a change in the size of the airways. In this case the increase in air flow is made possible by a proportionately increased airway pressure, the resistance remaining, therefore, unaltered. However, if the CO_2 did constrict the airways, an even higher pressure would be needed in order to maintain the increased flow rate. In that instance the calculated resistance will be raised, and this is apparently the case in our control subjects. However, in the patients with mitral stenosis the CO_2 stimulation caused threefold increase in ventilation with no change in the measured total lung resistance. This phenomenon was somewhat surprising, taking into consideration the initially raised total lung resistance while breathing room air. The possibility exists that in the patients the CO_2 causes an increased ventilatory drive alone, and the resulting hyperventilation is made possible by concomitant and proportionate rise of pressure in the bronchial tree; thus the total lung resistance remains unchanged. The fact that the ventilatory response is lower in these patients than in the controls may be explained either by the diminished responsiveness of the respiratory centre to CO_2 or by the presence of an initially increased total lung resistance, or by both. However, if one assumes that CO_2 inhalation has an identical effect on the bronchi in patients and in normal subjects, the unchanged total lung resistance of the patients may be explained by their inability to increase the transpulmonary pressure to the same extent. This inability may be related to diminished mechanical properties of the lung or respiratory muscles and to reduced cardiac performance.

Our patients suffered from mitral stenosis of moderate degree. As pointed out in the classification of the subject material, they exhibited clinical, radiographic, and electrocardiographic evidence of predominant stenosis of the mitral valve, and were handicapped in their physical activity. It is known that such patients, at this stage of the disease, do have a reduced elasticity of the lungs, and a raised airway resistance as a result of the long-standing pulmonary congestion. Furthermore, they are limited in physical effort, at least partly, because of lack of concomitant rise of cardiac output according to need. Moreover, the cost of breathing is also higher than in healthy subjects. Under these conditions the finding that patients with mitral stenosis are able to hyperventilate their lungs only to such a degree as can be reached without raising the transpulmonary pressure gradient above that prevailing at rest may be explained by their reduced pulmonary mechanics and diminished cardiac performance. Whether patients in the earlier stages of mitral stenosis would react similarly to healthy subjects, or whether patients with more advanced mitral valve disease would hyperventilate even less than those studied, was not clarified in the present investigation.

SUMMARY

Arterial blood gases, pulmonary ventilation, and mechanics of breathing were studied in 6 healthy subjects and in 8 patients with mitral stenosis. These parameters were measured while breathing room air and during inhalation of 5 per cent CO_2 in oxygen for 18 minutes.

In the healthy subjects there was a fourfold increase in minute volume and significant rise in the total lung resistance, with no change in lung compliance, following CO_2 stimulation.

In patients with mitral stenosis, CO_2 inhalation resulted in a threefold increase in minute ventilation. The total lung resistance, which was initially much raised, did not change following inhalation of the gas mixture.

The possible mechanisms regarding the effect of CO_2 on the mechanics of breathing in health and in mitral stenosis are discussed.

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